MicroRNA-217: A regulator of human cancer

Shuai Zhou[1], Chao Zhu[1], Qing Pang, Hui Chun Liu*

Department of Hepatobiliary Pancreatic Surgery, The First Affiliated Hospital of Bengbu Medical College, Anhui, 233000, China

ARTICLEINFO

Keywords:
mircoRNA-217 Cancer
Target gene
oncomiR
Tumor suppressor miRNA

ABSTRACT

As highly conserved non-coding RNAs of approximately 18–24 nucleotides, microRNAs (miRNAs) regulate the expression of target genes. Multiple studies have demonstrated that miRNAs participate in the regulation of human cancer. MircoRNA-217 (miR-217) participates in the regulation of various tumors by specifically binding target genes and post-transcriptional regulation. In recent years, there have been numerous reports about miR- 217 in tumor progression. MiR-217 is known mainly as a tumor suppressor, although some studies have shown that it functions as an oncomiR. Here, we review the current research related to miR-217, including its role in tumor progression and the molecular mechanisms.

1. Introduction

Cancer has become a serious threat to human health due to its characteristics of concealed symptoms and recurrence. In 2019, there were 1,762,450 new cancer cases and 606,880 deaths in the United States [1]. Therefore, the identification of cancer-related targets or pathways and the development of targeted therapies that can effectively kill cancer cells have become a focus of research. MicroRNAs (miRNAs) are highly conserved non-coding RNAs comprising 18–24 nucleotides [2]. MiRNAs regulate the expression of target genes by binding to the 3′-UTR the untranslated region. A single miRNA can regulate multiple targets, and target genes are regulated by multiple miRNAs [3]. While miRNAs are ubiquitous in eukaryotic cells and highly conserved in different species, their expression in tissues and binding to target genes are both highly specific [4]. MiRNAs are involved in the regulation of various processes, including cell proliferation, invasion, metastasis, and apoptosis, and play a key role in cancer [5–8]. According to their different functions, miRNAs are divided into pro-cancer and anti-cancer factors. For example, miR-552 binds to p53 to promote the progression of laryngeal cancer [9]. In contrast, the progression of colorectal cancer can be inhibited via the miR-328-3P/PIS3K/AKT axis [10]. In recent years, researchers have focused on the relationship between miRNAs and tumors and potential biomarkers of tumor development have been identified.

MicroRNA-217 (miR-217), which was first reported in 2007, is located in the human chromosomal region 2q16.2, and can be used to distinguish normal pancreas, chronic pancreatitis, and pancreatic cancer (PC) [11]. MiR-217 regulates transcription in pancreatic cancer cells to influence disease progression [12]. Furthermore, miR-217 inhibits the N-methyl-d-aspartic acid receptor and regulates the development of vascular smooth muscle cells [13]. MiR-217 is also positively correlated with the severity of diabetic nephropathy [14]. Although miR-217 is has been identified as a tumor suppressor in multiple cancers, some studies have verified its function as an oncomiR [21,52,72–74]. Accumulating evidence indicates that miR-217 plays a regulatory role in cancer development. In this review, we systematically summarize the expression, function, target genes, interacting molecules, and application prospects of miR-217 in various cancers.

2. MiR-217 function is cancer type-dependent

Advances in gene sequencing technology have yielded numerous reports suggesting that miR-217 inhibits tumor proliferation, metastasis, invasion, and epithelial-mesenchymal transition (EMT), and promotes apoptosis. The expression of miR-217 is regulated by many lncRNAs and circRNAs via the ceRNA mechanism [15]. The interactions between upstream regulators and miR-217 are summarized in Table 1 and Fig. 1. The expression and effects of miR-217 in various cancers are summarized in Table 2 and Fig. 1.

2.1. MiR-217 and hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a severe disease that threatens human health. Therefore, finding a specific biomarker of HCC is **Table 1**

* Corresponding author.
E-mail addresses: zs172116108@163.com (S. Zhou), 2018031287@stu.bbmc.edu.cn (C. Zhu), portxiu2@126.com (Q. Pang), liuhcdoctor@126.com (H.C. Liu). [1]Equal contribution.

https://doi.org/10.1016/j.biopha.2020.110943
Received 28 June 2020; Received in revised form 17 October 2020; Accepted 25 October 2020
Available online 27 November 2020
0753-3322/© 2020 Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Summary of miR-217 interactions in human cancers.

Type of cancer	Upstream regulator
Hepatocellular carcinoma	lncRNA HOTAIR lncRNA CRNDE circular RNA MAN2B2
Pancreatic adenocarcinoma	lncRNA MALAT1 circular RNA ADAM9
Gastric cancer	lncRNA HOTAIR
Colorectal cancer	lncRNA CRNDE lncRNA KCNQ1OT1
Lung cancer	lncRNA MALAT1 lncRNA LINC01614 has_circ_0023404
Glioma	lncRNA HOTAIR circular RNA TTBK2
Osteosarcoma	lncRNA HOTAIR
Esophageal squamous cell carcinoma	lncRNA MALAT1 hsa_circ _100367
Renal cell carcinoma	lncRNA HOTAIR
Bladder cancer	hsa_circ_0000144
Malignant melanoma	lncRNA XIST

significant for its treatment. In 2014, Jing et al. reported that miR-217 expression was decreased in the MHCC-97H cell line and 48 HCC tissues compared with the levels detected in other cell lines (Huh-7, HepG2, SMMC7721 and MHCC-97 H). Moreover, miR-217 inhibited the invasion and metastasis of HCC by suppressing the expression of E2F3 protein [16]. In 2017, Mao et al. demonstrated that miR-217 inhibited the proliferation, migration, and invasion progression of HCC cells and induced apoptosis by inhibiting expression of the target gene *MTDH*, and a 582-amino acid single pass transmembrane protein [17]. In 2018, Li et al. found that lncRNA HOTAIR promoted the proliferation, metastasis, and invasion of HCC by sponging miR-217. It has been confirmed that miR-217 is downregulated in HCC cells [18]. The lncRNA CRNDE/miR-217/MAPK1 axis is involved in the regulation of invasion, metastasis and proliferation of HCC [19]. The level of lncRNA CRNDE was found to be negatively correlated with miR-217 expression. High expression of miR-217 inhibited the expression of MAPK1 and reduced HCC cell proliferation [19]. Furthermore, miR-217 is regulated by circular RNA MAN2B2, and is expressed at low levels in HepG2 and Huh-7 cells and inhibits HCC proliferation and metastasis by combining with MAPK1 [20]. Although previous studies demonstrated that miR-217 is downregulated in HCC cells, miR-217 was found to be highly expressed in 64 HCC tissues and seven HCC cell lines. Moreover, miR-217 promotes the characteristics of HCC stem cells by inhibiting DKK1, which acts as an important negative regulator of the Wnt/β-catenin signaling pathway [21].

Although these studies showed that miR-217 inhibits the growth of HCC cells, further evaluation of a large number of clinical samples is still required for validation.

2.2. MiR-217 and PC

PC is a major threat to human health, with a very low 5-year survival rate (<5%) because many patients have no obvious symptoms [22]. Finding potential therapeutic targets for pancreatic cancer is a top priority [23]. In 2007, researchers found that miR-217 and miR-196a were highly expressed in PC cell lines and could be used as potential biomarkers to distinguish normal pancreatic tissue, pancreatitis and PC [11]. In 2010, Wu-Gan et al. found that miR-217 was significantly lower in 21 pancreatic ductal adenocarcinoma cancer (PDAC) tissues and seven cell lines (PANC-1, MIAPaCa-2, AsPC-1, BxPC-3, P1, P3 and P7). In PDAC tissues, miR-217 is predominantly expressed in the nuclei of the ductal epithelia cells, and reduces PDAC cell proliferation by inhibiting the *KRAS* oncogene [24]. In 2104, researchers demonstrated that miR-217 inhibits the EMT process in chronic pancreatitis and PC via silent information regulator 2 homolog 1 (SIRT1) [25]. Mir-217 is not only downregulated in 30 PC tissues and the AsPC-1 cell line, but also binds to Tpd5212, and inhibits cell proliferation, invasion and metastasis via the PIK3CA/AKT signaling pathway [26]. It has also been shown that miR-217 is negatively correlated with the actin-binding protein anillin (ANLN), and reduces the invasion capacity of PDCA cells [27]. Analysis of the molecules that interact with miR-217 showed

Table 2

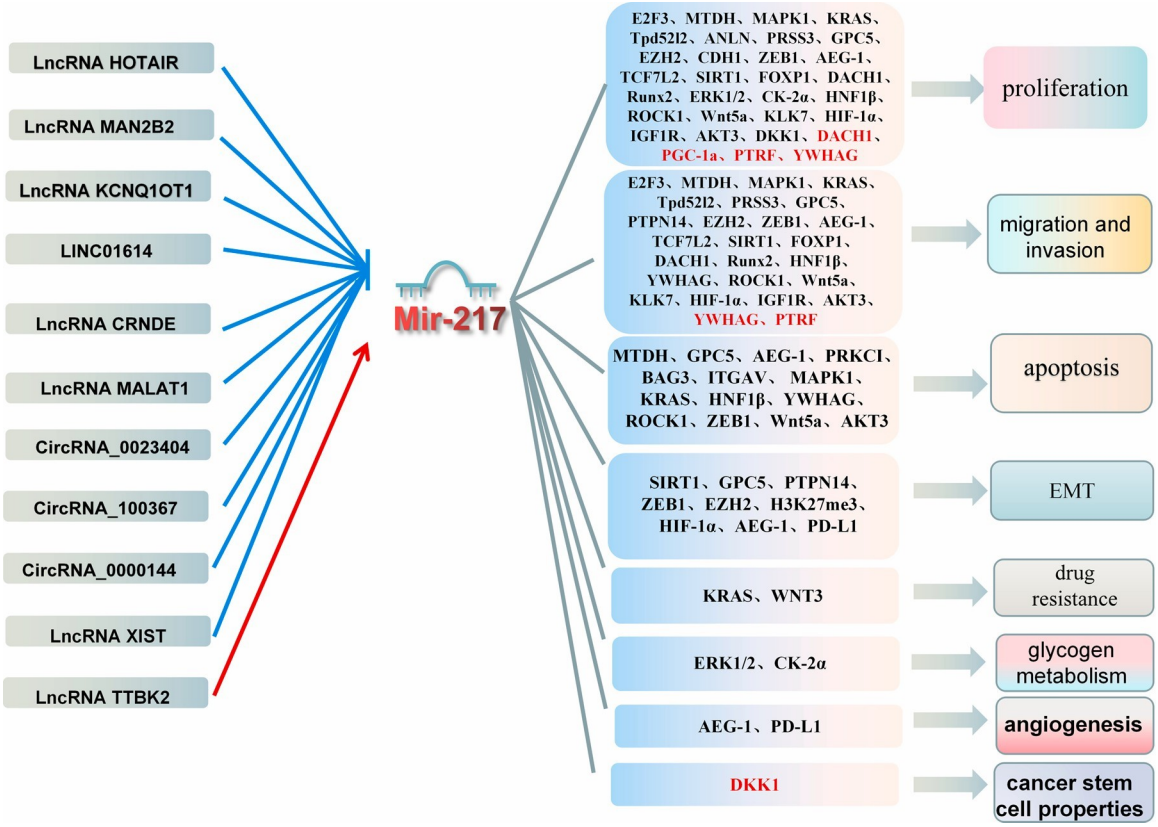

Fig. 1. Mechanisms by which miR-217 regulates cancer progression at the molecular level.

Types of cancer	Expression	Target gene	Pathway	Functions	Source
Hepatocellular carcinoma	DOWN	E2F3	/	Suppressed proliferation, invasion and migration	[16]
	DOWN	MTDH	/	Suppressed proliferation, migration, and invasion, and induced apoptosis	[17]
	DOWN	/	/	Suppressed proliferation, migration and invasion	[18]
	DOWN	MAPK1	/	Suppressed proliferation, invasion and migration	[19]
	DOWN	MAPK1	/	Suppressed proliferation, invasion and migration	[20]
	UP	DKK1	Wnt/ β-catenin	Promotes cancer stem cell properties	[21]
Pancreatic adenocarcinoma	DOWN	/	/	/	[11]
	DOWN	KRAS, MAPK1	/	Suppressed proliferation, invasion and migration	[24]
	DOWN	SIRT1	/	Suppressed EMT	[25]
	DOWN	Tpd52l2	PIK3CA/AKT	Suppressed proliferation, invasion and migration	[26]
	DOWN	ANLN	/	Suppressed proliferation	[27]
	DOWN	KRAS	/	Suppressed proliferation	[28]
	DOWN	PRSS3	ERK/VEGF	Suppressed proliferation, invasion and migration	[29]
	DOWN	EZH2	/	Suppressed proliferation, invasion and migration	[30]
	DOWN	GPC5	/	Suppressed proliferation, invasion, migration, induced apoptosis	[31]
	DOWN	GPC5	/	Suppressed proliferation and invasion	[32]
	DOWN	PTPN14	/	Suppressed invasion, migration, and EMT	[33]
	DOWN	CDH1	/	Suppressed proliferation	[34]
Colorectal cancer	DOWN	AEG-1	/	Suppressed proliferation, migration and invasion, and induced apoptosis	[36]
	DOWN	MAPK1	MAPK	Suppressed proliferation and induced apoptosis	[37]
	DOWN	PRKCI, BAG3 ITGAV, MAPK1	ERK-MAPK	Induced apoptosis	[38]
	DOWN	TCF7L2	Wnt/ β-catenin	Suppressed proliferation, migration and invasion	[39]
	DOWN	ZEB1	/	Suppressed proliferation, invasion, migration and EMT	[40]
Lung cancer	DOWN	KRAS	PI3K/AKT	Suppressed proliferation, migration and invasion, induced apoptosis, and increased the sensitivity to cisplatin	[42]
	DOWN	SIRT1	p53/KAI1	Suppressed proliferation, migration and invasion	[43]
	DOWN	EZH2, H3K27me3	/	Suppressed EMT	[44]
	DOWN	FOXP1	/	Suppressed proliferation, invasion and migration	[45]
	DOWN	ZEB1	/	Suppressed proliferation, invasion, migration, and EMT	[46]
	DOWN	DACH1	/	Suppressed proliferation, invasion and migration	[47]
Glioma	DOWN	Runx2	/	Suppressed proliferation, migration and invasion	[49]
	DOWN	ERK1/2, CK-α	MAPK	Suppressed glycogen metabolism	[50]
	DOWN	HNF1β	PI3K/AKT, ERK	Suppressed proliferation, migration, and invasion, and induced apoptosis	[51]
	UP	YWHAG	MDM4/p53	Promoted proliferation, migration and invasion	[52]
Cervical cancer	DOWN	ROCK1	/	Suppressed proliferation, migration and invasion, and induced apoptosis	[55]
	DOWN	KRAS	/	Suppressed proliferation, migration and invasion, induced apoptosis, and increased the sensitivity to cisplatin	[56]
	DOWN	MAPK1	/	Suppressed proliferation, migration and invasion, and induced apoptosis	[57]
Osteosarcoma	DOWN	WASF3	/ /	Suppressed proliferation, migration and invasion	[58]
	DOWN	Wnt5a	/	Suppressed proliferation, migration and invasion, and induced apoptosis	[59]
	DOWN	SETD8		Suppressed proliferation and invasion	[60]
	DOWN	SIRT1	/	Suppressed proliferation, migration, invasion, and EMT	[61]
	DOWN	ZEB1	NF-κB/iNOS	Suppressed proliferation, migration and invasion, and induced apoptosis	[62]
Esophageal cancer	DOWN	KLK7	/	Suppressed proliferation and invasion	[64]
	DOWN	/	/	Suppressed proliferation, migration and invasion	[65]
	DOWN	WNT3	/	Increased sensitivity to cisplatin	[66]
Renal cell carcinoma	DOWN	HIF-1α	HIF-1α/AXL	Suppressed proliferation, migration invasion, and EMT	[67]
Bladder cancer	DOWN	RUNX2	/	Suppressed proliferation and invasion	[68]
Epithelial ovarian carcinoma	DOWN	IGF1R	/	Suppressed proliferation, migration and invasion	[69]
Thyroid cancer	DOWN	AKT3	/	Suppressed proliferation, migration, and invasion, and induced apoptosis	[70]
Laryngeal cancer	DOWN	AEG-1 P, PD-L1	/	Suppressed migration, invasion, EMT and angiogenesis	[71]
Breast cancer	UP	DACH1 PGC-1a	/	Promoted proliferation	[72]
	UP		/	Promoted proliferation	[73]
Cutaneous squamous cell carcinoma	UP	PTRF	/	Promoted proliferation and invasion	[74]
Malignant melanoma	DOWN	/	/	Suppressed proliferation, and migration	[75]

Summary of miR-217 expression and its functions in human cancers.

that the lncRNA MALAT1/miR-217/KRAS axis promotes the development, proliferation, and metastasis of PCDA cell lines. LncRNA MALAT1 inhibits the transfer of miR-217 from the nucleus to the cytoplasm [28].

In 2019, Xing el al. verified that the circular RNA ADAM9/miR-217/PRSS3 axis promotes PC progression via the ERK/VEGF signaling pathway. PRSS3, an atypical subtype of trypsinogen, is highly expressed in PC and plays an oncogenic role [29].

In summary, these studies confirm that miR-217 plays an anticancer role in PC cells and implicates it as a potential molecular therapeutic target.

2.3. MiR-217 and gastric cancer (GC)

GC is another most common tumor of the gastrointestinal system and is the third leading cause of cancer-related deaths worldwide [1]. Therefore, it is very important to find suitable diagnostic and therapeutic targets. In 2015, miR-217 was found to be expressed at low levels in 83 cancer samples and was shown to inhibit the proliferation of GC cells by targeting *EZH2* [30]. In the same year, Wang et al. showed that miR-217 was downregulated in 50 GC tissues and that the 3′-UTR terminal of miR-217 binds to *GPC5* to reduce GC cell invasion and metastasis [31]. LncRNA HOTAIR is highly expressed in GC cells and inhibits miR-217 expression by via the ceRNA mechanism. The lncRNA HOTAIR/miR-217/GPC5 axis promotes the proliferation and EMT of GC cells [32]. In 2019, Gen et al. discovered that miR-217 can combine with protein tyrosine phosphatase non-receptor type 14 (PTPN14) to reduce proliferation and EMT of GC cells [33]. In 2018, researchers verified that miR-217 was highly expressed in exosomes from 67 GC patients, negatively correlated with CDH1, and promoted GC cell proliferation and metastasis. CDH1, a transmembrane glycoprotein that plays a crucial role in maintaining cell-cell adhesion, acts as a tumor suppressor gene in GC [34].

In summary, more and more studies have demonstrated that miR- 217 functions as an important anticancer gene in GC cells. However, more research is required to confirm the functional role of miR-217 in GC.

2.4. MiR-217 and colorectal cancer (CRC)

In developing countries, the prevalence of CRC is increasing year by year, and the association between miRNAs and CRC has been confirmed [35]. It has been reported that the long-term survival rate of CRC patients with low expression of miR-217 is low. Furthermore, miR-217 expression is negatively correlated with astrocyte elevated gene-1 (AEG-1) expression and promotes the proliferation and invasion of CRC cells [36]. In 2016, Nan et al. demonstrated that the low expression of miR-217 in 121 cancer tissues inhibited both proliferation and invasion of CRC cells by targeting MAPK. Kaplan–Meier survival and Cox regression analyses showed that the prognosis of the group of patients with low expression of miR-217 was far worse than that of the group with high expression [37]. In 2017, researchers found that miR-217 promotes CRC cell apoptosis by targeting PRKCI, BAG3, ITGAV, and MAPK1 via the ERK-MAPK signaling pathway [38]. LncRNA CRNDE, which functions as a molecular sponge of miR-217, is highly expressed in CRC cells. MiR-217 inhibits the proliferation of CRC cells by targeting TCF7L2 via the WNT/β-catenin signaling pathway [39]. In 2019, Yinzhu et al. demonstrated that the lncRNA KCNQ1OT1/miR-217/ZEB1 axis promoted the proliferation and EMT of CRC cells [40]. These studies implicate miR-217 as a potential molecular target for CRC.

2.5. MiR-217 and lung cancer

Lung cancer is a serious threat to human health due to its high aggressiveness and potential for metastasis [41]. *KRAS*, which is a well-known oncogene that is highly expressed in lung cancer, can promote its proliferation and reduce its sensitivity to cisplatin. MiR-217 can combine with *KRAS* to inhibit its effect [42]. In lung cancer, miR-217 inhibits the proliferation and metastasis of pc-14/B cells by targeting SIRT1. SIRT1 inhibits p53, KAI1/CD82, matrix metalloproteinase 9 (MMP-9), and beta-catenin, but upregulates E-cadherin protein expression [43]. The lncRNA MALAT1/miR-217/EZH2/H3K27me3 axis can promote the EMT process in lung cancer [44]. In addition, cigarette smoke extract (CSE) can reduce miR-217 levels in bronchial epithelial cells [44]. MiR-217 expression is negatively correlated with both LINC01614 and FOXP1, which are highly expressed in cancer and have been shown to regulate the progression of non-small cell lung cancer (NSCLC) [45]. The has_circ_0023404/miR-217/ZEB1 axis promotes the proliferation and metastasis of NSCLC, while miR-217 is expressed at low levels in NSCLC cells [46]. Similarly, the lncRNA HOTAIR/miR-217/DACH1 axis enhances the development of NSCLC cells [47].

In summary, miR-217 plays the role of tumor suppressor in NSCLC.

2.6. MiR-217 and glioma

Accompanied by high rates of recurrence and metastasis, glioma is the most common malignant brain cancer [48]. MiR-217 is downregulated in glioma, and miR-217 overexpression inhibits the proliferation, invasion and metastasis of glioma by targeting Runt-

related transcription factor 2 (Runx2) [49]. MiR-217 inhibits the level of mGluR1 in gangliogliomas and increases glycogen accumulation by targeting the binding of ERK1/2 and CK-2a through the MAPK signaling pathway [50]. The circular RNA TTBK2 is negatively correlated with miR-217, while miR-217 targets and binds to hepatocyte nuclear factor-1beta (HNF-1β) to promote glioma cell proliferation, invasion and metastasis, and inhibit apoptosis. HNF-1β inhibits tumor cell apoptosis by binding to the promoter of *Derlin-1* [51]. In contrast, miR-217 was highly expressed in 41 glioblastoma (GBM) specimens and four cell lines, and promoted the proliferation and invasion of GBM by targeted binding to *YMHAG* [52]. Interestingly, miR-217 acts as an oncogene in glioma, but a tumor suppressor gene in glioblastoma. However, the exact mechanisms remain to be elucidated.

2.7. MiR-217 and cervical cancer (CC)

CC occurs with a high incidence worldwide, and is a threat to women's health; therefore, the identification of targeted therapeutic sites is urgently required [53,54]. MiR-217 was found to be poorly expressed in 165 clinical samples and multiple cell lines, and inhibits CC cell proliferation, metastasis and invasion through targeted binding of Rho-associated protein kinase 1 (ROCK1), KRAS, and MAPK. By combining with the *KRAS* gene, miR-217 can reduce the sensitivity of CC cells to cisplatin [55–57].

These studies suggest that miR-217 plays an important role as an anticancer gene in CC.

2.8. MiR-217 and osteosarcoma

Osteosarcoma is the most common bone tumor, especially in children and adolescents. In vitro studies showed that miR-217 inhibited the proliferation, invasion, and metastasis of osteosarcoma by combining with WASF3, Wnt5a, SET domain-containing protein 8 (SETD8), and SIRT1 [58–61]. WASF3, which is a member of the Wiskott–Aldrich family of synthetic proteins, promotes actin aggregation to participate in tumor cell metastasis [58]. Wnt5a is involved in the differentiation, proliferation, and apoptosis of tumor cells [59]. SETD8 promotes the proliferation and invasion of tumor osteosarcoma cells [60]. SIRT1 increases the expression and function of n-cadherin to promote EMT of osteosarcoma cells [61]. In addition, lncRNA HOTAIR, is highly expressed in multiple cancers. In osteosarcoma, lncRNA HOTAIR acts as a molecular sponge of miR-217 to reduce miR-217 expression and promote the proliferation of osteosarcoma cells. MiR-217 knockdown also reduces binding to ZEB1 to promote the proliferation of osteosarcoma cells [62].

In summary, miR-217 functions as a tumor suppressor gene in osteosarcoma.

2.9. MiR-217 and esophageal cancer (EC)

EC is one of the most common causes of death worldwide [1]. Cigarette smoke condensate is considered to be relevant to lung cancer [63]. Studies have revealed that cigarette smoke condensate reduces the expression of miR-217 (by targeting with KLK7) and promotes the progression of EC [64]. In addition, lncRNA MALAT1 can reduce miR-217 levels and promotes the apoptosis and proliferation of esophageal squamous cell carcinoma (ESCC) cell by activating P21, P27, MIA2, ROBO1, CTHC1, and CCT4 and inhibiting B-MYB [65]. The circRNA-100367/miR-217/WNT3 axis can improve the sensitivity of ESCC cells to radiotherapy. MiR-217 expression is negatively correlated with circRNA-100367 [66] and WNT3 was identified as the target gene of miR-217 [66].

In summary, miR-217 functions as an anticancer gene in the development of EC.

2.10. MiR-217 and other cancers

In 2017, Hong et al. demonstrated that the lncRNA HOTAIR/miR- 217/HIF-1α/AXL axis increased migration, apoptosis and EMT of renal cell carcinoma (RCC) cells. MiR-217 expression was negatively correlated with HOTAIR and targeted HIF-1α [67]. Huang et al. showed that circular RNA 0000144 was expressed at high levels in 69 bladder cancer cells, and its expression was reduced by binding to miR-217 in the form of a ceRNA. MiR-217 binds RUNX2 to inhibit the proliferation and metastasis of bladder cancer [68]. As a downstream molecule of miR-217, IGF1R promotes the proliferation of epithelial ovarian carcinoma cells [69]. MiR-217 was found to be downregulated in 58 cases of thyroid cancer, and inhibited the proliferation of thyroid cancer cells by binding to downstream AKT3 (a key molecule of the AKT signaling pathway) [70]. In 2017, Miao et al. discovered low levels of miR-217 expression in 29 laryngeal cancer tissues and Hep2 cells. Activation of the miR-217/Hep2/PD-L1 axis inhibited EMT and angiogenesis of Hep2 cells [71]. In contrast, miR-217 acts as an oncogene in breast cancer. Zhang et al. reported

that miR-217 was highly expressed in 39 breast cancer tissues and MDA-MB-231, MCF-7, T47D, AND MDA-MB-468 cells. MiR-217 also inhibited breast cancer proliferation by binding directly to DACH1 [72]. MiR-217 binds to its the target gene *PGC-1* to promote the proliferation of MCF-7 and MDA-MB-231 cells [73]. PTRF is poorly expressed in cutaneous squamous cell carcinoma (cSCC) cells and inhibits their proliferation. However, miR-217 combines with *PTRF* to promote the proliferation and invasion of cSCC cells [74]. LncRNA XIST can inhibit the expression of miR-217 by acting as a molecular sponge, and promoting the progression of malignant melanoma [75].

MiR-217 is inhibited by lncRNA HOTAIR, lncRNA MAN2B2 and other genes, while its expression is promoted by lncRNA TTBK2. MiR- 217 can inhibit cancer cell proliferation, metastasis, invasion, EMT, chemotherapy resistance, and angiogenesis, and induce apoptosis, via *E2F3* and other genes. In contrast, the combination of miR-217 with the *DACH1*, *PCG-1A*, *PTRF*, and *YWHAG* genes to promote cancer cell proliferation. MiR-217 binds with *YWHAG* and *PTRF* to promote cancer invasion and migration. In addition, miR-217 can combine with *DKK1* to promote cancer stem cell properties.

3. The contradictory role of miR-217

The consequences of altered miR-217 expression are related to enhanced or repressed cell proliferation, invasion, metastasis, apoptosis, EMT, drug resistance, glycogen metabolism, angiogenesis, and stem cell properties in cancers. MiR-217 can function as an oncomiR or a tumor suppressor. Analysis of the expression profiles showed that expression of the majority of targets was negatively correlated with miR-217. However, in HCC, miR-217 can promote the CSC-like phenotype of the tumor through *DKK1* targeting, leading to the activation of the Wnt signaling pathway. The miR-217/YWHAG/MDM4/p53 signaling pathway promotes the expression of glioblastoma tissues. In breast cancer and cutaneous squamous cell carcinoma, miR-217 functions as an oncogene to promote the expression of carcinoma tissues. We consider that the dual effects of miR-217 may be explained by differences in tissue subtypes and the abundance of targets.

3.1. Different histological subtypes

Different tissue subtypes and cell lines may contribute to the differential expression of miR-217 in the same type of cancer. For example, Chunlin et al. found that miR-217 is highly expressed in, and promoted the characteristics of HCC tumor hepatocytes. However, miR-217 is expressed at low levels in highly invasive MHCC-97H HCC and metastatic HCC. Most importantly, miR-217 is expressed at low levels in glioma and high levels in glioblastoma, suggesting differential expression of miR-217 in different tumor tissue subtypes.

3.2. The dual role of target genes

Each miRNA can regulate a large number of targeted mRNAs through base pairing, and miR-217 can regulate gene expression in different cancers by targeting multiple mRNAs. Moreover, these targets can also be regulated by other miRNAs, besides miR-217. Although many reports confirmed that miR-217 targets many genes, the identity of all its targets in different cancers remain to be elucidated. One study demonstrated that *PGC-1A* (miR-217 as its upstream activation factor) functions as a tumor suppressor gene in breast cancer, while other studies showed that *PGC-1A* was significantly increased in breast cancer specimens and was positively correlated with clinical staging [73,76]. These findings provide evidence of the dual role of *PGC-1A* in cancer.

In summary, miR-217 plays a dual role in cancer. We speculate that this phenomenon is due to the effects of different cancer subtypes and the dual role of target genes, although the specific mechanism of action requires further exploration.

4. Conclusions

In summary, miR-217 is poorly expressed in most cancers, but is highly expressed in breast cancer, glioblastoma, and cutaneous squamous cell carcinoma. We hypothesize that the differences in tumor subtypes and multiple actions of target genes may account for the dual roles of miR-217 in different cancers, although the specific mechanisms of action are unknown. In vitro studies have revealed that miR-217 is involved in the regulation of tumor cell proliferation, metastasis, invasion, apoptosis, EMT, drug resistance and other processes, thus indicating that miR-217 plays a dual role in cancer progression.

There are several suggestions for future research as follows: (1) The sample size of differentially expressed cancers is small and not persuasive; therefore, analysis of a large number of samples is required to determine the

role of miR-217 in various cancers. (2) The regulatory networks of molecules upstream of miR-217, such as lncRNAs and circRNAs, also need further investigation. (3) More evidence is still required to verify the target gene network of miR-217. (4) The role of miR-217 in different cancers still should be validated before specific target studies can be developed.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

This study was funded by the Anhui Provincial Natural Science Foundation for Outstanding Youth (2008085J37), the First Affiliated Hospital of Bengbu Medical College Science Fund for Distinguished Young Scholars (2019byyfyjq05), and the National Nature Science Foundation of China (Grant No. 81600452).

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2019, CA Cancer J. Clin. 69 (1) (2019) 7–34, https://doi.org/10.3322/caac.21551.
[2] J.J. Kwon, T.D. Factora, S. Dey, J. Kota, A systematic review of miR-29 in cancer, Mol. Ther. Oncol. 12 (2019) 173–194, https://doi.org/10.1016/j.omto.2018.12.011.
[3] E. Karamitopoulou, S. Haemmig, U. Baumgartner, C. Schlup, M. Wartenberg, E. Vassella, MicroRNA dysregulation in the tumor microenvironment influences the phenotype of pancreatic cancer, Mod. Pathol. 30 (8) (2017) 1116–1125, https://doi.org/10.1038/modpathol.2017.35.
[4] D.P. Bartel, MicroRNAs: target recognition and regulatory functions, Cell 136 (2) (2009) 215–233, https://doi.org/10.1016/j.cell.2009.01.002.
[5] Y. Toiyama, Y. Okugawa, J. Fleshman, C. Richard Boland, A. Goel, MicroRNAs as potential liquid biopsy biomarkers in colorectal cancer: a systematic review, Biochim. Biophys. Acta Rev. Cancer 1870 (2) (2018) 274–282, https://doi.org/10.1016/j.bbcan.2018.05.006.
[6] F. Ma, M. Liu, B. Tang, C.Y. Zhang, Sensitive quantification of MicroRNAs by isothermal helicase-dependent amplification, Anal. Chem. 89 (11) (2017) 6182–6187, https://doi.org/10.1021/acs.analchem.7b01113.
[7] M.X. Sha, X.W. Huang, Q. Yin, MiR-548b-3p inhibits proliferation and migration of breast cancer cells by targeting MDM2, Eur. Rev. Med. Pharmacol. Sci. 24 (6) (2020) 3105–3112, https://doi.org/10.26355/eurrev_202003_20675.
[8] Y. Shi, Z. Liu, Serum miR-92a-1 is a novel diagnostic biomarker for colorectal cancer, J. Cell. Mol. Med. 24 (2020) 8363–8367, https://doi.org/10.1111/ jcmm.15282.
[9] J. Gu, T. Han, L. Sun, A.H. Yan, X.J. Jiang, miR-552 promotes laryngocarcinoma cells proliferation and metastasis by targeting p53 pathway, Cell Cycle (2020) 1–10, https://doi.org/10.1080/15384101.2020.1743910.
[10] S. Pan, F. Ren, L. Li, et al., MiR-328-3p inhibits cell proliferation and metastasis in colorectal cancer by targeting Girdin and inhibiting the PI3K/Akt signaling pathway, Exp. Cell Res. 390 (1) (2020) 111939, https://doi.org/10.1016/j.yexcr.2020.111939.
[11] A.E. Szafranska, T.S. Davison, J. John, et al., MicroRNA expression alterations are linked to tumorigenesis and non-neoplastic processes in pancreatic ductal adenocarcinoma, Oncogene 26 (30) (2007) 4442–4452, https://doi.org/10.1038/sj.onc.1210228.
[12] C. Blenkiron, K.J. Askelund, S.T. Shanbhag, et al., MicroRNAs in mesenteric lymph and plasma during acute pancreatitis, Ann. Surg. 260 (2) (2014) 341–347, https://doi.org/10.1097/SLA.0000000000000447.
[13] H. Duan, Y. Li, L. Yan, et al., MicroRNA-217 suppresses homocysteine-induced proliferation and migration of vascular smooth muscle cells via N-methyl-D-aspartic acid receptor inhibition, Clin. Exp. Pharmacol. Physiol. 43 (10) (2016) 967–975, https://doi.org/10.1111/1440-1681.12611.
[14] Y. Shao, H. Ren, C. Lv, X. Ma, C. Wu, Q. Wang, Changes of serum MiR-217 and the correlation with the severity in type 2 diabetes patients with different stages of diabetic kidney disease, Endocrine 55 (1) (2017) 130–138, https://doi.org/10.1007/s12020-016-1069-4.
[15] A.S. Bayoumi, A. Sayed, Z. Broskova, et al., Crosstalk between long noncoding RNAs and MicroRNAs in health and disease, Int. J. Mol. Sci. 17 (3) (2016) 356, https://doi.org/10.3390/ijms17030356.
[16] J. Su, Q. Wang, Y. Liu, M. Zhong, miR-217 inhibits invasion of hepatocellular carcinoma cells through direct suppression of E2F3, Mol. Cell. Biochem. 392 (1–2) (2014) 289–296, https://doi.org/10.1007/s11010-014-2039-x.
[17] M. Zhang, M. Li, N. Li, et al., miR-217 suppresses proliferation, migration, and invasion promoting apoptosis via targeting MTDH in hepatocellular carcinoma, Oncol. Rep. 37 (3) (2017) 1772–1778, https://doi.org/10.3892/or.2017.5401.
[18] L.P. Wang, J.P. Wang, X.P. Wang, HOTAIR contributes to the growth of liver cancer via targeting miR-217, Oncol. Lett. 15 (5) (2018) 7963–7972, https://doi.org/10.3892/ol.2018.8341.
[19] H. Wang, J. Ke, Q. Guo, K.P. Barnabo Nampoukime, P. Yang, K. Ma, Long non-coding RNA CRNDE promotes the proliferation, migration and invasion of hepatocellular carcinoma cells through miR-217/MAPK1 axis, J. Cell. Mol. Med. 22 (12) (2018) 5862–5876, https://doi.org/10.1111/jcmm.13856.
[20] X. Fu, J. Zhang, X. He, et al., Circular RNA MAN2B2 promotes cell proliferation of hepatocellular carcinoma cells via the miRNA-217/MAPK1 axis, J. Cancer 11 (11) (2020) 3318–3326. https://10.7150/jca.36500.
[21] C. Jiang, M. Yu, X. Xie, et al., miR-217 targeting DKK1 promotes cancer stem cell properties via activation of the Wnt signaling pathway in hepatocellular carcinoma, Oncol. Rep. 38 (4) (2017) 2351–2359, https://doi.org/10.3892/ or.2017.5924.
[22] S.P. Pereira, L. Oldfield, A. Ney, et al., Early detection of pancreatic cancer, Lancet Gastroenterol. Hepatol. 5 (7) (2020) 698–710, https://doi.org/10.1016/S2468-1253(19)30416-9.
[23] X. Zhang, H. Li, T. Zhen, Y. Dong, X. Pei, H. Shi, hsa_circ_001653 implicates in the development of pancreatic ductal adenocarcinoma by regulating MicroRNA-377- mediated HOXC6 Axis, Mol. Ther. Nucleic Acids 20 (2020) 252–264, https://doi.org/10.1016/j.omtn.2019.12.028.

[24] W.G. Zhao, S.N. Yu, Z.H. Lu, Y.H. Ma, Y.M. Gu, J. Chen, The miR-217 microRNA functions as a potential tumor suppressor in pancreatic ductal adenocarcinoma by targeting KRAS, Carcinogenesis 31 (10) (2010) 1726–1733, https://doi.org/ 10.1093/carcin/bgq160.
[25] S. Deng, S. Zhu, B. Wang, et al., Chronic pancreatitis and pancreatic cancer demonstrate active epithelial-mesenchymal transition profile, regulated by miR- 217-SIRT1 pathway, Cancer Lett. 355 (2) (2014) 184–191, https://doi.org/ 10.1016/j.canlet.2014.08.007.
[26] Q. Chen, P. Wang, Y. Fu, et al., MicroRNA-217 inhibits cell proliferation, invasion and migration by targeting Tpd52l2 in human pancreatic adenocarcinoma, Oncol. Rep. 38 (6) (2017) 3567–3573, https://doi.org/10.3892/or.2017.6036.
[27] T. Idichi, N. Seki, H. Kurahara, et al., Regulation of actin-binding protein ANLN by antitumor miR-217 inhibits cancer cell aggressiveness in pancreatic ductal adenocarcinoma, Oncotarget 8 (32) (2017) 53180–53193, https://doi.org/ 10.18632/oncotarget.18261.
[28] P. Liu, H. Yang, J. Zhang, et al., The lncRNA MALAT1 acts as a competing endogenous RNA to regulate KRAS expression by sponging miR-217 in pancreatic ductal adenocarcinoma, Sci. Rep. 7 (1) (2017) 5186, https://doi.org/10.1038/ s41598-017-05274-4.
[29] C. Xing, H. Ye, W. Wang, et al., Circular RNA ADAM9 facilitates the malignant behaviours of pancreatic cancer by sponging miR-217 and upregulating PRSS3 expression, Artif. Cells Nanomed. Biotechnol. 47 (1) (2019) 3920–3928, https:// doi.org/10.1080/21691401.2019.1671856.
[30] D.L. Chen, D.S. Zhang, Y.X. Lu, et al., microRNA-217 inhibits tumor progression and metastasis by downregulating EZH2 and predicts favorable prognosis in gastric cancer, Oncotarget 6 (13) (2015) 10868–10879, https://doi.org/10.18632/ oncotarget.3451.
[31] H. Wang, X. Dong, X. Gu, R. Qin, H. Jia, J. Gao, The MicroRNA-217 functions as a potential tumor suppressor in gastric cancer by targeting GPC5, PLoS One 10 (6) (2015) e012547, https://doi.org/10.1371/journal.pone.0125474.
[32] X. Dong, X. He, A. Guan, et al., Long non-coding RNA Hotair promotes gastric cancer progression via miR-217-GPC5 axis, Life Sci. 217 (2019) 271–282, https:// doi.org/10.1016/j.lfs.2018.12.024.
[33] G. Chen, Z. Yang, M. Feng, Z. Wang, microRNA-217 suppressed epithelial-to-mesenchymal transition through targeting PTPN14 in gastric cancer, Biosci. Rep. 40 (1) (2020), https://doi.org/10.1042/BSR20193176. BSR20193176.
[34] W. Li, Y.Q. Gao, MiR-217 is involved in the carcinogenesis of gastric cancer by down-regulating CDH1 expression, Kaohsiung J. Med. Sci. 34 (7) (2018) 377–384, https://doi.org/10.1016/j.kjms.2018.02.003.
[35] M. Honari, R. Shafabakhsh, R.J. Reiter, H. Mirzaei, Z. Asemi, Resveratrol is a promising agent for colorectal cancer prevention and treatment: focus on molecular mechanisms, Cancer Cell Int. 19 (2019) 180, https://doi.org/10.1186/ s12935-019-0906-y.
[36] B. Wang, Z.L. Shen, K.W. Jiang, et al., MicroRNA-217 functions as a prognosis predictor and inhibits colorectal cancer cell proliferation and invasion via an AEG- 1 dependent mechanism, BMC Cancer 15 (2015) 437, https://doi.org/10.1186/ s12885-015-1438-z.
[37] N. Zhang, C. Lu, L. Chen, miR-217 regulates tumor growth and apoptosis by targeting the MAPK signaling pathway in colorectal cancer, Oncol. Lett. 12 (6) (2016) 4589–4597, https://doi.org/10.3892/ol.2016.5249.
[38] M. Flum, M. Kleemann, H. Schneider, et al., miR-217-5p induces apoptosis by directly targeting PRKCI, BAG3, ITGAV and MAPK1 in colorectal cancer cells, J. Cell Commun. Signal. 12 (2) (2018) 451–466, https://doi.org/10.1007/s12079- 017-0410-x.
[39] B. Yu, X. Ye, Q. Du, B. Zhu, Q. Zhai, X.X. Li, The long non-coding RNA CRNDE promotes colorectal carcinoma progression by competitively binding miR-217 with TCF7L2 and enhancing the Wnt/β-catenin signaling pathway, Cell. Physiol. Biochem. 41 (6) (2017) 2489–2502, https://doi.org/10.1159/000475941.
[40] Y. Bian, G. Gao, Q. Zhang, et al., KCNQ1OT1/miR-217/ZEB1 feedback loop facilitates cell migration and epithelial-mesenchymal transition in colorectal cancer, Cancer Biol. Ther. 20 (6) (2019) 886–896, https://doi.org/10.1080/ 15384047.2019.1579959.
[41] L. Wang, Z. Hu, Q. Guo, L. Yang, Y. Pang, W. Wang, MiR-23b functions as an oncogenic miRNA by downregulating Mcl-1S in lung cancer cell line A549, J. Biochem. Mol. Toxicol. (2020) e22494, https://doi.org/10.1002/jbt.22494.
[42] J. Guo, Z. Feng, Z. Huang, H. Wang, W. Lu, MicroRNA-217 functions as a tumour suppressor gene and correlates with cell resistance to cisplatin in lung cancer, Mol. Cells 37 (9) (2014) 664–671, https://doi.org/10.14348/molcells.2014.0121 .
[43] W. Jiang, L. Hou, J. Wei, et al., Hsa-miR-217 inhibits the proliferation, migration and invasion in non-small-cell lung cancer cells via targeting SIRT1 and p53/KAI1 signaling, Balkan Med. J. 37 (2020) 208–214, https://doi.org/10.4274/ balkanmedj.galenos.2020.2019.9.91.
[44] L. Lu, F. Luo, Y. Liu, et al., Posttranscriptional silencing of the lncRNA MALAT1 by miR-217 inhibits the epithelial-mesenchymal transition via enhancer of zeste homolog 2 in the malignant transformation of HBE cells induced by cigarette smoke extract, Toxicol. Appl. Pharmacol. 289 (2) (2015) 276–285, https://doi.org/ 10.1016/j.taap.2015.09.016.
[45] A.N. Liu, H.J. Qu, C.Y. Yu, P. Sun, Knockdown of LINC01614 inhibits lung adenocarcinoma cell progression by up-regulating miR-217 and down-regulating FOXP1, J. Cell. Mol. Med. 22 (9) (2018) 4034–4044, https://doi.org/10.1111/ jcmm.13483.
[46] C. Liu, Z. Zhang, D. Qi, Circular RNA hsa_circ_0023404 promotes proliferation, migration and invasion in non-small cell lung cancer by regulating miR-217/ZEB1 axis, Onco Targets Ther. 12 (2019) 6181–6189, https://doi.org/10.2147/OTT. S201834.
[47] S.S. Chen, M. Peng, G.Z. Zhou, et al., Long non-coding RNA HOTAIR regulates the development of non-small cell lung cancer through miR-217/DACH1 signaling pathway, Eur. Rev. Med. Pharmacol. Sci. 23 (2) (2019) 670–678, https://doi.org/ 10.26355/eurrev_201901_16905.
[48] J. Lin, J.A. Bytnar, B.J. Theeler, K.A. McGlynn, C.D. Shriver, K. Zhu, Survival among patients with glioma in the US Military Health System: a comparison with patients in the Surveillance, Epidemiology, and End Results Program, Cancer 126 (13) (2020) 3053–3060, https://doi.org/10.1002/cncr.32884.
[49] Y. Zhu, H. Zhao, L. Feng, S. Xu, MicroRNA-217 inhibits cell proliferation and invasion by targeting Runx2 in human glioma, Am. J. Transl. Res. 8 (3) (2016) 1482–1491. https://pubmed.ncbi.nlm.nih.gov/27186274.
[50] A. Majumdar, F. Ahmad, T. Sheikh, et al., miR-217-casein kinase-2 cross talk regulates ERK activation in ganglioglioma, J. Mol. Med.

(Berl.) 95 (11) (2017) 1215–1226, https://doi.org/10.1007/s00109-017-1571-z.
[51] J. Zheng, X. Liu, Y. Xue, et al., TTBK2 circular RNA promotes glioma malignancy by regulating miR-217/HNF1β/Derlin-1 pathway, J. Hematol. Oncol. 10 (1) (2017) 52, https://doi.org/10.1186/s13045-017-0422-2.
[52] H. Wang, H. Zhi, D. Ma, T. Li, MiR-217 promoted the proliferation and invasion of glioblastoma by repressing YWHAG, Cytokine 92 (2017) 93–102, https://doi.org/10.1016/j.cyto.2016.12.013.
[53] Q. Cao, N. Wang, L. Ren, J. Tian, S. Yang, H. Cheng, miR-125a-5p post- transcriptionally suppresses GALNT7 to inhibit proliferation and invasion in cervical cancer cells via the EGFR/PI3K/AKT pathway, Cancer Cell Int. 20 (2020) 117, https://doi.org/10.1186/s12935-020-01209-8.
[54] X. Gu, M. Dong, Z. Liu, J. Yang, Y. Shi, MiR-499a-5p inhibits proliferation, invasion, migration, and epithelial-mesenchymal transition, and enhances radiosensitivity of cervical cancer cells via targeting eIF4E, Onco Targets Ther. 13 (2020) 2913–2924, https://doi.org/10.2147/OTT.S241631.
[55] J. Dong, M. Wang, D. Ni, et al., MicroRNA-217 functions as a tumor suppressor in cervical cancer cells through targeting Rho-associated protein kinase 1, Oncol. Lett. 16 (5) (2018) 5535–5542, https://doi.org/10.3892/ol.2018.9335.
[56] Z. Yin, W. Ren, MicroRNA-217 acts as a tumor suppressor and correlates with the chemoresistance of cervical carcinoma to cisplatin, Onco Targets Ther. 12 (2019) 759–771, https://doi.org/10.2147/OTT.S176618.
[57] L. Zhu, S. Yang, J. Wang, miR-217 inhibits the migration and invasion of HeLa cells through modulating MAPK1, Int. J. Mol. Med. 44 (5) (2019) 1824–1832, https://doi.org/10.3892/ijmm.2019.4328.
[58] L. Shen, P. Wang, J. Yang, X. Li, MicroRNA-217 regulates WASF3 expression and suppresses tumor growth and metastasis in osteosarcoma, PLoS One 9 (10) (2014) e109138, https://doi.org/10.1371/journal.pone.0109138.
[59] R. Wei, Z. Deng, J. Su, miR-217 targeting Wnt5a in osteosarcoma functions as a potential tumor suppressor, Biomed. Pharmacother. 72 (2015) 158–164, https://doi.org/10.1016/j.biopha.2015.04.012.
[60] G. Yang, J. Wang, B. Huang, Loss of miR-217 promotes osteosarcoma cell proliferation through targeting SETD8, Pharmazie 73 (12) (2018) 711–714, https://doi.org/10.1691/ph.2018.8644.
[61] S. He, Z. Wang, H. Tang, J. Dong, Y. Qu, J. Lv, MiR-217 inhibits proliferation, migration, and invasion by targeting SIRT1 in osteosarcoma, Cancer Biother. Radiopharm. 34 (4) (2019) 264–270, https://doi.org/10.1089/cbr.2017.239.
[62] B. Wang, X.L. Qu, J. Liu, J. Lu, Z.Y. Zhou, HOTAIR promotes osteosarcoma development by sponging miR-217 and targeting ZEB1, J. Cell. Physiol. 234 (5) (2019) 6173–6181, https://doi.org/10.1002/jcp.27394.
[63] N. Babu, J. Advani, H.S. Solanki, et al., miRNA and proteomic dysregulation in non-small cell lung cancer in response to cigarette smoke, Microrna 7 (1) (2018) 38–53, https://doi.org/10.2174/2211536607666180103165343.
[64] S. Xi, S. Inchauste, H. Guo, et al., Cigarette smoke mediates epigenetic repression of miR-217 during esophageal adenocarcinogenesis, Oncogene 34 (44) (2015) 5548–5559, https://doi.org/10.1038/onc.2015.10.
[65] X. Wang, M. Li, Z. Wang, et al., Silencing of long noncoding RNA MALAT1 by miR- 101 and miR-217 inhibits proliferation, migration, and invasion of esophageal squamous cell carcinoma cells, J. Biol. Chem. 290 (7) (2015) 3925–3935, https://doi.org/10.1074/jbc.M114.596866.
[66] J. Liu, N. Xue, Y. Guo, et al., CircRNA_100367 regulated the radiation sensitivity of esophageal squamous cell carcinomas through miR-217/Wnt3 pathway, Aging (Albany NY) 11 (24) (2019) 12412–12427, https://doi.org/10.18632/ aging.102580.
[67] Q. Hong, O. Li, W. Zheng, et al., LncRNA HOTAIR regulates HIF-1α/AXL signaling through inhibition of miR-217 in renal cell carcinoma, Cell Death Dis. 8 (5) (2017) e2772, https://doi.org/10.1038/cddis.2017.181.
[68] W. Huang, Y. Lu, F. Wang, X. Huang, Z. Yu, Downregulation of circular RNA hsa_circ_0000144 inhibits bladder cancer progression via stimulating miR-217 and suppressing RUNX2 expression, Gene 678 (2018) 337–342, https://doi.org/10.1016/j.gene.2018.08.036.
[69] J. Li, D. Li, W. Zhang, Tumor suppressor role of miR-217 in human epithelial ovarian cancer by targeting IGF1R, Oncol. Rep. 35 (3) (2016) 1671–1679, https://doi.org/10.3892/or.2015.4498.
[70] Y. Lin, K. Cheng, T. Wang, et al., miR-217 inhibits proliferation, migration, and invasion via targeting AKT3 in thyroid cancer, Biomed. Pharmacother. 95 (2017) 1718–1724, https://doi.org/10.1016/j.biopha.2017.09.074.
[71] S. Miao, X. Mao, S. Zhao, et al., miR-217 inhibits laryngeal cancer metastasis by repressing AEG-1 and PD-L1 expression, Oncotarget 8 (37) (2017) 62143–62153, https://doi.org/10.18632/oncotarget.19121.
[72] Q. Zhang, Y. Yuan, J. Cui, T. Xiao, D. Jiang, MiR-217 promotes tumor proliferation in breast cancer via targeting DACH1, J. Cancer 6 (2) (2015) 184–191, https://doi.org/10.7150/jca.10822.
[73] S. Zhang, X. Liu, J. Liu, H. Guo, H. Xu, G. Zhang, PGC-1 alpha interacts with microRNA-217 to functionally regulate breast cancer cell proliferation, Biomed. Pharmacother. 85 (2017) 541–548, https://doi.org/10.1016/j.biopha.2016.11.062.
[74] M. Bai, M. Zhang, F. Long, N. Yu, A. Zeng, X. Wang, MiR-217 promotes cutaneous squamous cell carcinoma progression by targeting PTRF, Am. J. Transl. Res. 9 (2) (2017) 647–655. https://pubmed.ncbi.nlm.nih.gov/28337292/.
[75] Y. Zhang, J. Liu, Y. Gao, Z. Zhang, H. Zhang, Long noncoding RNA XIST acts as a competing endogenous RNA to promote malignant melanoma growth and metastasis by sponging miR-217, Panminerva Med. 12 (13) (2019) 03746–03747, https://doi.org/10.23736/S0031-0808.19.03746-7.
[76] F.F. Cai, C. Xu, X. Pan, et al., Prognostic value of plasma levels of HIF-1a and PGC- 1a in breast cancer, Oncotarget 7 (47) (2016) 77793–77806, https://doi.org/10.18632/oncotarget.12796.